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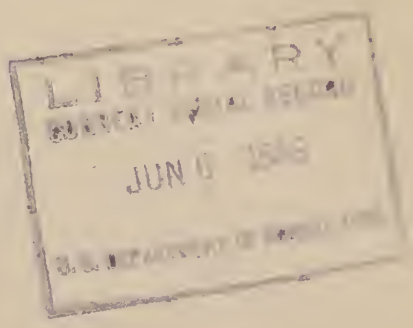

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THE CHEMISTRY AND THERAPEUTIC USE OF RUTIN

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Rutin, $C_{27}H_{30}O_{16} \cdot 3H_2O$, is a glucoside derived from flavonol. It occurs as a tasteless yellow nontoxic powder consisting of masses of microscopic needle crystals that become plastic between 185° and 192° C and decompose at 214°-215° C. Rutin has been reported as a constituent of 38 species of plants, among which may be mentioned buckwheat (**Fagopyrum esculentum**), tobacco (**Nicotiana tabacum**), forsythia (**Forsythia spendens** and **fortunei**), hydrangea (**Hydrangea paniculata**) and pansies (**Viola sp.**).

Rutin is slightly soluble in cold water, approximately 0.13 g. per liter at 20°, and much more soluble in boiling water, from which it may readily be recrystallized. It is more soluble in methanol, ethanol, acetone, and ethyl acetate, and very soluble in formamide, pyridine and alkaline solutions. It is insoluble in chloroform, ether, benzene, and petroleum solvents. On exposure to light, rutin gradually darkens, and should be preserved out of contact with daylight.

On hydrolysis with dilute acids, rutin yields quercetin, glucose, and rhamnose:

$$C_{27}H_{30}O_{16} + 2\ H_2O = C_{15}H_{10}O_7 + C_6H_{12}O_6 + C_6H_{12}O_5$$

No toxic effects have been observed with rutin. Experiments in progress by the Pharmacology Laboratory of this Bureau and studies by the Bureau of Animal Industry as well as reports by foreign investigators have not indicated the presence of acute or chronic toxicity to laboratory animals. A large number of patients have been treated daily for periods up to 30 months without any evidence of toxic effects from rutin.

Sources of Rutin

At this Laboratory high-quality flue-cured tobacco was originally used as a source of rutin. It was later found that the buckwheat plant is a much better source, being considerably cheaper than tobacco and containing eight to twelve times as much of the glucoside. The content of rutin varies with the age of the buckwheat plant, being highest at the 3- to 5-blossom stage and decreasing as the plant matures. When the plant has gone to seed, it contains very little rutin. When the harvested plant is slowly dried, there is a large loss of rutin, so that rapid drying by a special process must be resorted to if the dried plant is desired for use in preparing the glucoside. Recently harvested buckwheat may be used if facilities for prompt handling are available.

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry Agricultural Research Aominstration.United States Department of Agriculture

Preparation of Rutin

Rutin may be extracted either from fresh or dried buckwheat. Three processes for the extraction have been developed at this Laboratory. Two of these are described in a publication dealing with the specially dried plant. Extraction of rutin from fresh buckwheat is briefly described here.

The fresh plant, without being cut into small pieces, is macerated in alcohol for 24 hours. Denatured alcohol may be used if desired. At the end of this period, the solution is drawn off and replaced by fresh alcohol, which is allowed to stand for a further 24 hours and then drawn off. The two solutions will contain 95 to 97 percent of the rutin in the plant. The alcohol is distilled from the solution, and the resulting residue, which consists of a suspension of fats in a solution of rutin and other plant constituents, is cooled and the rutin is crystallized. The mixture of fat and rutin is filtered, dried, and extracted with benzene to remove the fats. The crude rutin is recrystallized twice from water and refined through alcohol, silica gel being used to remove extraneous pigments, if desirable.

A convenient method for recrystallization that has been successful in this Laboratory is conducted as follows: Rutin (10 g.) is dissolved in hot alcohol (50 ml.), and the solution is diluted to 500 ml. with water and filtered if necessary. On standing, the solution deposits flocculent masses of crystalline rutin, which may be filtered by suction, washed with cold water, and dried at 110°.

Pharmacology of Rutin and Flavonols

The pharmacology of the flavonols has not been studied extensively. These substances are of negligible toxicity, rutin appearing to be quite nonpoisonous, and they do not cause apparent reactions when administered to experimental animals. Cumulative action has not been observed.

A few reports, however, have appeared in the literature. Griffith, Couch and Lindauer have reported that rutin restores increased capillary fragility to normal in man and Scarborough has recently confirmed this observation. Sokoray and Czimmer reported that quercitrin causes a lowering of blood pressure, and Armentano confirmed this and showed that certain other flavonols and their glucosides, but not flavones, also reduce the blood pressure. Armentano, however, did not use rutin in his experiments.

The action of the flavonols on the isolated frog's heart has been reported by Czimmer, who studied rutin, and by von Jeney and Czimmer, who studied quercetin and quercitrin. Akamatsu has studied in addition myricetin and myricitrin. The action of the normal heart is increased, the force of the depressed heart is restored, the pulse is slowed, and the minute volume is increased. Armentano reported no increase in the heart volume.

Diuresis following the administration of flavonols has been reported by Akamatsu and Fukuda and Kono. Rutin combined with caffeine or theophylline increases the diuretic action in intensity and duration.

Von Jeney and his co-workers have reported that quercitrin decreases the normal respiratory metabolism in rats and antagonized the action of 2:4 dinitrophenol on this function.

Lavollay and Neumann reported that rutin, quercitrin, and naringin inhibit the autoxidation of adrenalin in the blood, thus prolonging its action. In hydrogen peroxide-peroxidase systems, the flavonols, but not the flavones, accelerate the oxidation of adrenalin. Preliminary injection of quercitrin prevents peptone shock.

Clinical Studies

Rutin was prepared in tablets for clinical study, each tablet containing 20 mg. of the glucoside. One tablet two or three times a day is the usual dose, but occasionally in refractory cases this dose has been increased severalfold.

The medical applications of rutin are based on its property of reducing increased capillary fragility to normal (Griffith, Couch and Lindauer, Proc. Soc. Exp. Biol. Med. 55: 228-9, 1944). Rutin has proved effective in certain hemorrhagic conditions in which capillary fragility or permeability is involved. The following analytical summary of clinical experience was prepared by Dr. J. Q. Griffith, Jr., of the Robinette Foundation, Medical School, University of Pennsylvania.

Altogether 1,219 cases were studied during the past 30 months. Of these, 255 cases, or 21 percent, had increased capillary fragility when measured according to the Gothlin technique. Rutin was administered to these patients in doses of from 60 to 120 mg. per diem. Only 29 patients required more than 60 mg. per diem. In no case was any toxic effect from the rutin observed, although one patient was allergic to buckwheat and the rutin had to be discontinued, crude hesperidin being substituted.

Of the 255 positive cases, there was an adequate follow-up in 173; the data quoted below refer to these 173 cases. Certain of these cases have been under observation for as long as 2-1/2 years.

In 152 cases (88 percent), the Gothlin index became permanently negative, indicating a return to normal capillary fragility. In 21 (12 percent), the Gothlin index either did not become negative or relapsed to positive after having become negative. Of these refractory cases, 15 were under observation for 6 months or less.

Twenty (11.5 percent) of the adequately studied cases had a history of apoplexy. In all of these the Gothlin index became negative, and there have been no further attacks.

Retinal hemorrhage had occurred in 20 cases (11.5 percent). In 17 of these cases (10 percent) the Gothlin index became permanently negative, while in three (1.5 percent) which have been under treatment for 4 months or less, the index has remained positive. Five patients have suffered further retinal hemmorhages, including four in whom the Goth lin index had become negative and one in whom it was still positive.

The incidence of increased capillary fragility according to sex was found to be: Males, 54 percent; females, 46 percent. It was distributed among age groups as follows:

Decade	Second	Third	Fourth	Fifth	Sixth	Seventh
Percent	3	11	30	30	22	4

The blood pressure was lowered in 63 cases (36 percent); in 52 instances the decrease was moderate, and in 11 (6 percent) there was a marked lowering.

In certain of the patients there was a definite improvement in symptoms. Of the cases studied, 72 (42 percent) showed no initial symptoms, 51 (30 percent) were definitely improved, 23 (13 percent) were probably improved, while there was no observable improvement in 27 (15 percent).

Rutin has been supplied to approximately 120 physicians, pharmacologists, and hospital clinics for medical use and study. A number of reports have been received from these collaborators, which may be summarized as follows:

Two reports state that rutin arrests the progress of diabetic retinitis. In one series of 50 cases, only 1 case failed to respond to treatment with rutin. Similar results were obtained in a second series of 5 cases.

Rutin is reported to be of value in offsetting the tendency of thiocyanate to increase capillary fragility, especially in the treatment of hypertension. Similarly, rutin may be used in combination with salicylates and arsenicals to preserve the capillary resistance at a normal level.

In two cases of unexplained pulmonary hemorrhage of long standing, the administration of rutin stopped the bleeding in about 3 weeks. Other hemorrhagic conditions due to capillary rupture have been reported benefited by rutin.

It has been emphasized that rutin should be continued even after the capillary fragility has returned to normal. Relapses following discontinuance of rutin have been reported and have cleared up on resumption of the drug. It has been stated that rutin is much less effective if there exists a simultaneous vitamin C deficiency. It is therefore recommended that care be taken to insure that the patient has an adequate intake of vitamin C.